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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BISBENZAMIDINES FOR THE TREATMENT OF PNEUMONIA



1,2-; 1,3-; or 1,4- disubstituted; R is selected from the group consisting of a hydrogen, a linear or branched alkyl group, containing from 1 to 20 carbon atoms; R' is selected from the group consisting of a hydrogen, a linear or branched alkyl group containing from one to twenty carbon atoms, an aromatic ring, a cycloalkyl group containing three to eight carbon atoms, or a hydroxyl group; alternatively, R and R' may form a cyclic structure that can be fused to another cyclic system; or a pharmaceutically acceptable salt thereof. Pharmaceutical formulations and active compounds useful in the practice of the present invention are also disclosed.

(57) Abstract: A method of combating infectious agents, such as *Pneumocystis pneumonia*, and a method of treating a subject in need of such treatment is disclosed. The method comprises administering to the subject a bis-benzamidine of formula (I) wherein the linker is a di-substituted cyclic moiety of any ring size and may contain at least one heteroatom; the aromatic group is

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/004468

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D295/14 C07D239/14 C07D235/30 C07D233/50 C07D233/02 C07D295/12 C07D317/28 C07D295/10 C07D403/12 C07D243/08 C07D401/10 C07C257/18 A61K31/551 A61K31/496 A61K31/4523 According to International Patent Classification (IPC) or to both national classification and IPC											
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D C07C Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BEILSTEIN Data, BIOSIS, CHEM ABS Data											
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;">Category *</th> <th style="width: 70%;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="width: 20%;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;"> WO 03/074476 A (TOYAMA CHEMICAL CO., LTD; HAYASHI, KAZUYA; OJIMA, KATSUJI; HORI, KOZO;) 12 September 2003 (2003-09-12) tables 3-6,8-12 </td> <td style="text-align: center; vertical-align: top;">1-48</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">P,X</td> <td style="vertical-align: top;"> ----- VANDEN EYNDE JEAN JACQUES ET AL: "Novel bisbenzamidines as potential drug candidates for the treatment of Pneumocystis carinii pneumonia." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS. 6 SEP 2004, vol. 14, no. 17, 6 September 2004 (2004-09-06), pages 4545-4548, XP002374421 ISSN: 0960-894X figure 2; table 1 ----- <div style="text-align: center;">-/--</div> </td> <td style="text-align: center; vertical-align: top;">17-19</td> </tr> </tbody> </table>			Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	WO 03/074476 A (TOYAMA CHEMICAL CO., LTD; HAYASHI, KAZUYA; OJIMA, KATSUJI; HORI, KOZO;) 12 September 2003 (2003-09-12) tables 3-6,8-12	1-48	P,X	----- VANDEN EYNDE JEAN JACQUES ET AL: "Novel bisbenzamidines as potential drug candidates for the treatment of Pneumocystis carinii pneumonia." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS. 6 SEP 2004, vol. 14, no. 17, 6 September 2004 (2004-09-06), pages 4545-4548, XP002374421 ISSN: 0960-894X figure 2; table 1 ----- <div style="text-align: center;">-/--</div>	17-19
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X	WO 03/074476 A (TOYAMA CHEMICAL CO., LTD; HAYASHI, KAZUYA; OJIMA, KATSUJI; HORI, KOZO;) 12 September 2003 (2003-09-12) tables 3-6,8-12	1-48									
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<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>											
<div style="display: flex;"> <div style="flex: 1;"> <p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="flex: 1;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>											
Date of the actual completion of the international search <div style="text-align: center;">30 March 2006</div>		Date of mailing of the international search report <div style="text-align: center;">25/04/2006</div>									
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center;">Sahagun Krause, H</div>									

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB2004/004468

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TAO BIN ET AL: "Synthesis and anti-Pneumocystis carinii activity of conformationally restricted analogues of pentamidine" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 34, no. 6, June 1999 (1999-06), pages 531-538, XP002374422 ISSN: 0223-5234 table 1	1-48
X	----- HUANG TIEN L ET AL: "N,N'-Bis(4-(N-alkylamidino)phenyl)homopip erazines as anti-Pneumocystis carinii agents" BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 11, no. 20, 22 October 2001 (2001-10-22), pages 2679-2681, XP002374423 ISSN: 0960-894X Scheme 1 table 1	1,13-16, 20-48
X	----- HUANG TIEN L ET AL: "Synthesis and anti-Pneumocystis carinii activity of piperidine-linked aromatic diimidazolines" BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 6, no. 17, 1996, pages 2087-2090, XP002374424 ISSN: 0960-894X Schemes 1 and 2	17
X	----- BOYKIN D W ET AL: "Dicationic diarylfurans as anti-Pneumocystis carinii agents." JOURNAL OF MEDICINAL CHEMISTRY. 17 MAR 1995, vol. 38, no. 6, 17 March 1995 (1995-03-17), pages 912-916, XP002374425 ISSN: 0022-2623 Chart 1	1
X	----- BOYKIN D W ET AL: "2,5-bis[4-(N-alkylamidino)phenyl]furans as anti-Pneumocystis carinii agents." JOURNAL OF MEDICINAL CHEMISTRY. 1 JAN 1998, vol. 41, no. 1, 1 January 1998 (1998-01-01), pages 124-129, XP002374426 ISSN: 0022-2623 table 1	1
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB2004/004468

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FRANCESCONI I ET AL: "2,4-Diphenyl furan diamidines as novel anti-Pneumocystis carinii pneumonia agents." JOURNAL OF MEDICINAL CHEMISTRY. 17 JUN 1999, vol. 42, no. 12, 17 June 1999 (1999-06-17), pages 2260-2265, XP002374427 ISSN: 0022-2623 Schemes 1 and 2	1
P,X	----- MAYENCE ANNIE ET AL: "Parallel solution-phase synthesis of conformationally restricted congeners of pentamidine and evaluation of their antiparasmodial activities." JOURNAL OF MEDICINAL CHEMISTRY. 6 MAY 2004, vol. 47, no. 10, 6 May 2004 (2004-05-06), pages 2700-2705, XP002374428 ISSN: 0022-2623 table 2	1-16, 20-48
E	----- WO 2005/033065 A (UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL; GEORGIA STATE UNIVERSITY) 14 April 2005 (2005-04-14) claims 2,3 -----	17-19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/004468

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 27-47 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-4, 13-17, 20-47 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 27-47 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 1-4, 13-17, 20-47 (part)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims 1-4, 13-17, 20-47 may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons, the search was performed taking into consideration the non-compliance in determining the extent of the search of claims 1-4, 13-17, 20-47.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-16, 20-48

Bisbenzamidine linked via a cyclic moiety

2. claims: 17-19

Bisbenzamides linked via a bis-(des)activated cyclic or
chain moiety

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB2004/004468

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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			BR 0308207 A	21-12-2004
			CA 2477212 A1	12-09-2003
			CN 1642906 A	20-07-2005
			EP 1481966 A1	01-12-2004
			NZ 534962 A	29-07-2005
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